

Review Article

Autophagy Intervened by MicroRNAs Causes Gliomas

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Abstract

miRNAs are found in organisms like animals, plants and a few viruses. They play a role in the modulation of post-transcriptional genome function and in the suppression of RNA. Glial cells, which support the functioning of the neuron (the alternative major type of brain cell), are the cause of brain tumors known as gliomas. Gliomagenesis is the process of the formation and growth of gliomas. A solitary miRNA has the ability to regulate several receptors at distinct stages of autophagy. Numerous miRNAs associated to autophagy were implicated in various phases of the development and advancement of carcinoma. These regulate a number of crucial metabolic processes, such as the cancer autophagic reflex. It has been observed that the activity of genes involved in gliomagenesis, tumor growth, proliferation, apoptosis and posttranscriptional control of anti-oncogenes is impacted by microRNA (miRNA) expression profile. Gliomas may thus deteriorate as a result of compromised miRNAs. The prognosis, therapeutic response and glioma origin may all be determined by miRNA profiling. miRNAs have the ability to be released into circulation and Cerebrospinal Fluid (CSF). They can also be transferred freely or via exosomes between normal and tumor cells, changing them into possible biomarkers for prognosis and/or diagnosis for gliomas.

Keywords: Autophagy; miRNAs; Glioma Tumors; Gliomagenesis

Abbreviations:

miRNAs: microRNA; GBM: Glioblastoma; GIC: Glioma Initiating Cells; TMZ: Temozolomide

Introduction

Autophagy is a self- degradative process that's important for balancing sources of energy at critical times in development and in response to nutrient stress [1]. Autophagy suppresses Tumor Progression in Gliomas. Autophagy has been demonstrated to inhibit the tumor inauguration stage, barring cancer cells during tumor progression [2]. Studies have demonstrated that miRNAs are pivotal controllers in the autophagy process, participating in several pathway of autophagy, including the upstream pathways that activate autophagy, the subsequent developmental stages and the later stage of degradation [3]. miRNAs are involved in various cancer processes like chemo resistance via interacting with their target mRNAs and suppressing their expression [4].

miRNAs have a distinct set of target genes and can modify most physiological processes, involving cell cycle checkpoints, cell survival and cell death mechanisms, affecting the growth, development and invasion of various cancers, including gliomas [5]. microRNAs are frequently deregulated in cancer and gliomas and their deregulation has been consorted with various aspects of glioma pathobiology [6].

Autophagy: A Brief Understanding

The field of autophagy research has developed swiftly since the first description of the process in the 1960s and the identification of autophagy genes in the 1990s [7]. Autophagy (tone- eating) is a conserved catabolic homeostatic procedure needed for cellular metabolic demands by removal of the damaged molecules and organelles and for release of stress constituted by pathology and infection [8]. Autophagy has been one of the most studied phenomena in cell biology and pathophysiology and bestowed its wide clinical implications, has become a healthy target for drug discovery [9].

Autophagy seems to be a 'double- sword' mechanism, hence, either its repression or inference could elevate neoplasm growth. Chemo and radiotherapy induce cellular stress in tumor cells with subsequent autophagy suppression. Simultaneously, it's claimed that the autophagy suppression increases chemo sensitivity in neoplastic cells [10]. Macroautophagy is a crucial homeostatic pathway that facilitates the degradation and recycling of cellular material [11]. The benefits of stimulating autophagy in disease have received increasing interest, for illustration, in the removal of protein aggregates contributing to neurodegeneration. In cancer, still, the role of autophagy appears to be more complex and depends on tumor stage, biology and the surrounding microenvironment [12].

Gliomagenesis

It is thought that glial cell genetic mutations (alterations) cause gliomas. Mutations in those cells' blueprint can cause aberrant tumor advancement, which would further proceed glioma to astrocytomas and finally glioblastoma (Fig. 1).

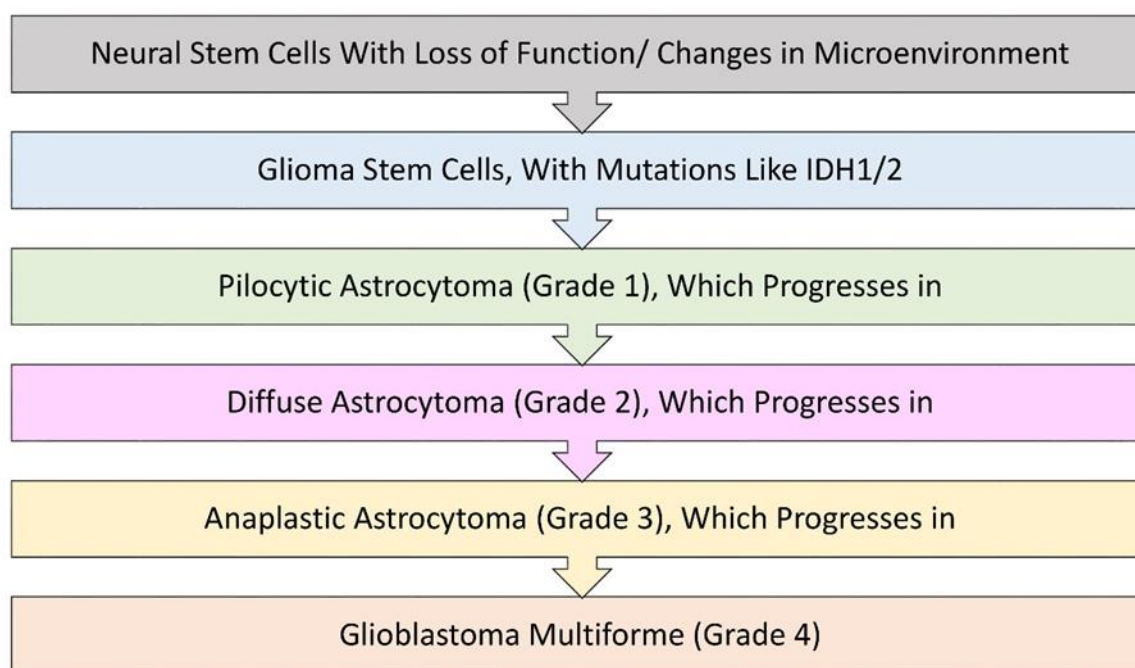


Figure 1: This figure represents the conversion of normal neural cells (neural stem cells to cancerous i.e., glioma stem cells and then progression of cancerous cells from stage one that is Pilocytic Astrocytoma to the most aggressive stage four that is the Glioblastoma Multiforme.

The higher advanced diagnostic stages of human gliomas are characterized by chromosomal fragility as well as the deletion and amplification of specific genes [13]. Oligodendrocyte Precursor Cells (OPCs) are often the site of adolescent gliomagenesis, with gliomas primarily emerging in the olfactory bulb the initial channel of the brain's olfactory network. Glioma progression is impacted by altering the function of Olfactory Receptor Neurons (ORNs) [14].

Genetically engineered models of astrocytomas imply that GBM growth may be facilitated by dysregulation of the processes that regulate gliomagenesis throughout healthy brain growth, including the division of Neural Stem Cells (NSCs) into astrocytes. These pathways comprise mechanisms that regulate the course of the cell cycle, like the ARF-MDM2-p53 and p16-CDK4-RB

pathways, as well as proliferation factor-induced signaling routes [15]. Gliomas may arise from Mendelian conditions which are primarily triggered by loss-of-function alterations in tumor suppressor genes, including Tau Protein p53 (TP53), Mismatch repair (MMR) genes and neurofibromin 1 (NF1) variants [16].

In gliomagenesis, autophagy plays two roles in an environment controlled by microRNA. High-grade gliomas expressed higher levels of LC3, AKT and miR-21 than low-grade gliomas did, but they expressed lower levels of ULK2. For ULK2 in low-grade gliomas, there was an average favorable association with PI3K, PTEN, ULK1, VPS34, mTOR, Beclin1, UVRAG, AKT and miR-374 and between AKT and ULK1, VPS34, UVRAG and miR-7. In high-grade gliomas, there had been a powerful positive association with mTOR, Beclin1, miR-30, miR-204, miR-374, miR-21 and miR-126 [17].

miRNAs and Their Roles

miRNAs were first discovered in the early 1990s, originally in the nematode worm *Caenorhabditis elegans*. latterly, they were set up to be preserved across species, pointing their elementary part in biology [18]. The discovery of miRNAs revolutionized our understanding of gene regulation, as they handed a method for fine- tuning gene expression beyond the more well- known transcriptional control [19].

The biogenesis of miRNAs involves a series of steps. originally, miRNA genes are transcribed into long primary miRNA (pri-miRNA) transcripts by RNA polymerase II. Pri- miRNAs are then reused in the nucleus by the microprocessor complex, conforming of the RNase III enzyme Droscha and its cofactor DGCR8, into shorter precursor miRNAs(pre-miRNAs). Pre-miRNAs are exported to the cytoplasm and further processed by another RNase III enzyme, Dicer, which cleaves them into mature miRNA duplexes [24]. One strand of the mature miRNA duplex, understood as the guide strand, is then loaded onto the RNA- convinced Silencing Complex (RISC), while the other strand, known as the passenger strand, is generally degraded [20].

miRNAs have a broad range of regulatory functions. They can impact cellular proceedings such as cell proliferation, differentiation, apoptosis and immune response. In development, miRNAs aid the precise timing and spatial distribution of gene expression, contributing to the conformation of tissues and organs. In the immune system, miRNAs play roles in immune cell development and response to infection and inflammation [21].

Autophagy and miRNAs

miRNAs can directly control autophagy- related proteins and pathways. miRNAs regulate autophagy in a diversity of cell types under distinct physiological conditions and in reaction to varied stress stimulants. While the identical miRNA may target diverse proteins in the autophagy pathway at once, different miRNAs reported to control degrees of the same key autophagy protein [22].

Among the several mechanisms that affect autophagy, microRNAs (miRNAs) play a pivotal part as gene controllers. Autophagy performs significant function in keeping up the homeostasis of miRNAs and miRNAs hold regulatory effects on autophagy both *in-vivo* and *in-vitro* due to their gene expression regulation effects on ATGs and proteins concerned in signaling pathways related to autophagy. Depending on whether the neoplasm cells are under metabolic or remedial stress, miRNAs- intermediated autophagy can have either pro-survival or pro-death effects [23].

Numerous microRNAs implicated in processes connected to autophagy. MiR-31, miR-34a, miR-9 and miR-101 have the ability to influence recycling and destruction. MicroRNAs 204, 183, 101 and 376b have an impact on autophagosomes [24].

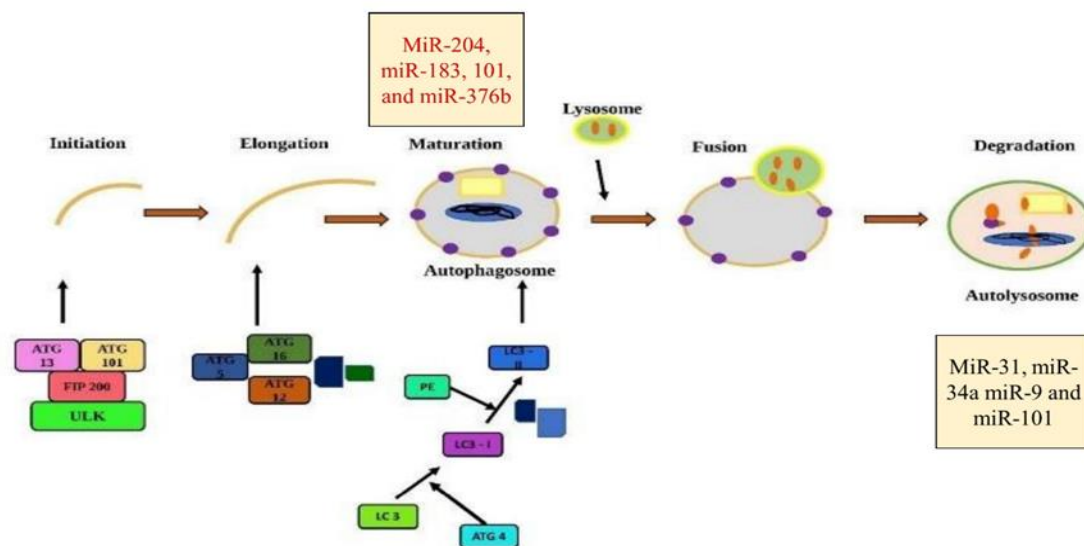


Figure 2: This figure represents the major steps of autophagy, where at two crucial checkpoints: first during the formation of autophagosome at the time of maturation stage and second during the degradation stage certain miRNAs play evident roles and support the regulation of autophagy pathway by controlling the functions of different Autophagy Related Genes.

Sr. No	MicroRNAs	Roles in GBM
1	miR-31	By suppressing STAT3 activation, miR-31 causes mitochondrial apoptosis and increases TMZ cytotoxicity in GBM cells [25]
2	miR-34a	A malignant inhibitor miRNA called miR-34a becomes reduced in GBM [26]
3	miR-9	In both in vivo and in vitro, GBM growth was inhibited by high expression of miR-9, which down regulated FOXP2. This was achieved through p21-dependent cell cycle arrest [27]
4	miR-101	By inhibiting GSK3 β in GBM, miR-101 can reverse TMZ resistance, providing a new and effective approach to GBM treatment [28]
5	miR-204	It was successfully demonstrated that miR-204 inhibits the invasion and carcinogenicity of a variety of cancer cells, involving glioma [29]
6	miR-183	MiR-183 expression promotes angiogenesis by upregulating HIF1A through IDH2 repression and inhibiting NEFL, which leads to an increase in mTOR and a worse prognosis [30]

Table 1: This table shows roles of some miRNA involved in autophagic pathways, which are related in causing or curing Glioblastoma Multiforme.

miRNAs in Cancer

These are the methods in which exosomal miRNAs control glioma cell growth. Exosomes produced by glioma cells are transferred to glioma cancer cells and exosomal miRNAs control the recipient cells' ability to proliferate. Exosomes have several ability medical uses, but one that has received a lot of attention is using them as nano-carriers to deliver proteins, small molecules and nucleic acids like miRNAs [31].

In cancer cells, the expression and function of miRNAs are frequently deregulated. This dysregulation can contribute to various aspects of cancer biology. There are many different types of miRNAs that play different roles in cancers.

Oncogenic MiRNAs: Some miRNAs portray as oncogenes when overexpressed in cancer. They target and hinder the expression of tumor suppressor genes or genes involved in apoptosis, cell cycle control and DNA repair. This promotes cancer cell survival and multiplication [32].

Tumor Suppressor: MiRNAs conversely, certain miRNAs act as tumor suppressors when they're under expressed or muted in cancer. These miRNAs generally target oncogenes or genes that promote cell proliferation [33].

Metastasis and Invasion: MiRNAs can control genes involved in cancer metastasis and invasion by modulating the expression of genes associated with Epithelial to Mesenchymal Transition (EMT) [34]. **Drug Resistance:** Dysregulated miRNAs can also contribute to cancer drug resistance by regulating the expression of drug transporters, anti- apoptotic proteins and drug target genes [35].

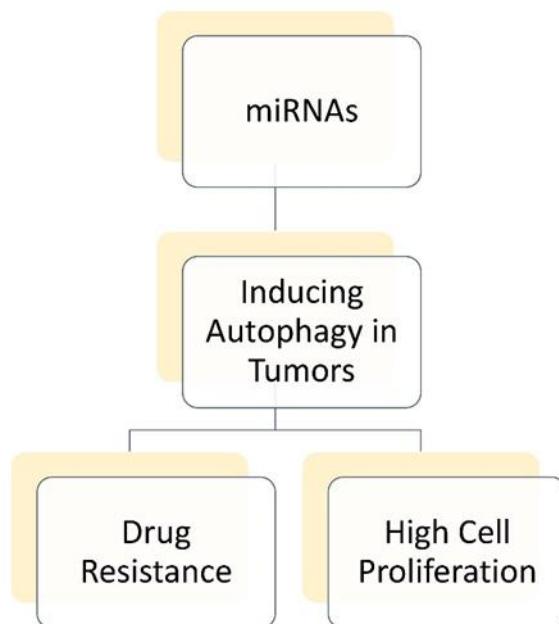


Figure 3: The above flowchart resembles that in cancerous cells, miRNA induce high autophagy by altering the pathway and facilitating autophagy related genes to carryout tumorigenesis by advancing cancer-cell proliferation and neoplasm growth and also promoting drug resistance in cancer cells.

miRNAs in Brain Tumors

miRNAs positively or negatively regulate tumor cell proliferation, apoptosis, migration, invasion, angiogenesis, acting on numerous target genes. MiRNAs are also involved in the regulation of glioma malignance and differentiation, pointing that deregulation of some miRNAs correlates with clinical prognosis [36].

Some miRNAs down- regulate the growth of glioblastoma and therefore, they may be used for therapy against this tumor. On the other hand, as various miRNAs support cell growth in glioblastoma, they might be considered as candidates for the stratification of poor prognostic glioblastoma [37].

The miRNA profile in GBM indicates the stage of the disease and can also facilitate the prognostic and selection of appropriate therapy. The diagnosis of GBM is also possible on the base of the analysis of miRNA from the blood and cerebrospinal fluid of cases. Functional analysis of respective GBM-specific miRNAs indicates that they can interpret as both oncogenes and tumor suppressors [38].

Autophagy Related miRNAs in Gliomas

Some of the important miRNAs associated with changes in autophagy pathways or Autophagy Related Genes that can cause gliomas are as follows:

1. miR21: The miR- 21 was actually first miRNA to be linked with glioma malignancy and is maybe the most researched miRNA in these neoplasms to date. Most reports image miR- 21 as an oncogenic miRNA. miR- 21 levels are elevated in human glioma cells and tissues as compared to normal glial cells and neurons [39]. It's affected in resistance against

chemo- and radiotherapy [40]. The formulation of LC3, AKT and miR- 21 was amplified in high- grade glioma compared to low- grade glioma while ULK2 expression was dropped in high- grade glioma [41]

2. miR-182: Oncogenomic assays discovered that miR- 182 is the only miRNA, out of 470 miRNAs pictured by The Cancer Genome Atlas (TCGA) agenda, which is associated with commendatory patient prognostic, neuro-developmental context, TMZ susceptibility and utmost significantly expressed in the least aggressive oligo-neural subdivision of GBM [42]. Suppression of Bcl2- like12 (Bcl2L12), c- Met and Hypoxia- Inducible Factor 2 α (HIF2A) is of central significance to miR- 182 anti-tumor activity, as it results in enhanced therapy susceptibility, dropped GIC sphere size, expansion and stemness *in-vitro* [43]
3. miR-450 a-5p: miR- 450a expression was significantly advanced in glioma tissues and cells than the normal tissues and cells and there's a favorable correlation between miR- 450a expression and histopathological grade of gliomas. In addition, the glioma patients with high miR- 450a expression displayed poorer prognostic. Downregulation of miR- 450a remarkably suppressed glioma cells growth *in vitro* and *in vivo* and inhibited glioma cells invasion and migration [44]. MiR- 450a- 5p displayed a negative correlation with the EGFR via targeting the 3' UTR of EGFR and regulated the EGFR-convincing PI3K/ AKT/ mTOR signaling pathway in glioma cells. thus, miR- 450a- 5p may serve as a tumor suppressor gene in glioma. By regulating the expression of miR- 450a- 5p in glioma, it may enhance the chemoresistance during glioma treatment. Also, combination treatment of miR- 450a- 5p and gefitinib also showed promoting apoptosis on normal glial cells [45]
4. miR-221/222: Overexpression of miR- 221 and miR- 222 is exposed in glioblastoma cells, which have multiple targets involved in gliomagenesis, including cell apoptosis. MiR-221/222 can control apoptosis by targeting the pro-apoptotic protein p53 (PUMA, p53 upregulated modulator of apoptosis) [46]. Knockdown of miR-221/222 increases apoptosis in human gliomas of diverse p53 types. low expression of miR-221/222 sensitized glioma cells to Temozolomide (TMZ). Down regulated miR-221/222 can sensitize glioma cells to TMZ by regulating apoptosis unaided of p53 status [47]
5. miR-451: One possible direct target of miRNA-451 in gliomas is IKK β . By using the luciferase assay, the effect of miRNA-451 overexpression on malignant glioma cell lines verified that IKK β is a target gene of miRNA-451. Targeting IKK β , MTT, cell invasion and wound-healing assays demonstrated substantial suppression of cell proliferation, invasion and migration in the LV-miRNA-451 group. The LV-miRNA-451 group exhibited a significant reduction in p-p65, Cyclin D1 and Ki67 expression, as demonstrated by immunohistochemistry. When combined, these findings imply that miRNA-451 may control the NF- κ B signaling pathway by focusing on IKK β , which both *in vitro* and *in vivo* inhibits the growth of glioma cells [48-54]

Apart from these, however there are many other miRNAs associated with gliomas.

Future Focus and Conclusion

miRNAs play a complex and multifaceted part in cancer by controlling gene expression. Dysregulation of miRNAs can route to the expansion and progression of cancer, framing miRNAs important players in cancer biology and potential targets for cancer diagnosis and therapy. Peculiar miRNA subsets may have potential diagnostic and prognostic values in some brain tumors. miRNA studies in cancer proceedings significantly improve current science on the pathogenesis of glioblastoma multiforme cells. miRNAs can act as substitute aims in diagnosis and therapeutics for gliomagenesis. Demonstrating the miRNA expression outline for diagnostic of GBM cells is an alternative to making a precise picture of the type and extent of cancerous changes in glioma cells. miRNAs have implications for glioma diagnosis, prognostic and treatment response prophecy. Their discovery in body fluids offers non-invasive individual chances. Exploiting miRNA expression or activity represents an implicit remedial approach. Still, additional study is needed to completely understand the functional roles of miRNAs and rephrase these findings into clinical practice. Modern molecular biological research aimed at determining the targets of individual miRNAs and their clusters will really permit in the future to attain fine regulation of signaling pathways, violations of which are associated with neoplastic processes. Therefore, it isn't difficult to anticipate that miRNA- based cancer therapeutics will be accelerated in the future decade.

In summary, as miRNAs play crucial role in the upregulation and downregulation of autophagy pathways and also provide sensitivity or chemoresistance to cancerous cells – thus, acting as for tumor inducing and tumor suppressing agents and also have contribution in determining the grades of glioma tumors, they should be researched more and used in molecular biology techniques as therapeutic agents.

Conflict of Interest

The authors have no conflict of interest to declare.

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